

mellitus but who themselves show no evidence of carbohydrate abnormality, have been studied. It has been possible to demonstrate readily that in such subjects average membrane thickness is significantly greater than in normal subjects, and moreover; in well over one-half of such prediabetic patients a statistically significant degree of basement membrane hypertrophy is present at the time of biopsy.^{5,6} These data would then lend further support to the suggestion that the carbohydrate abnormalities of diabetes mellitus do not cause the vascular disease of diabetes. They raise the possibility that the vascular disease of diabetes mellitus may actually represent an independent and perhaps a primary lesion of the diabetes syndrome.

In summary, electron microscopic studies both in hyperglycemic animals and in hyperglycemia of non-diabetic origin in man would indicate that elevations in blood glucose, even though severe and of long duration, do not themselves produce diabetic microangiopathy or capillary basement membrane thickening. On the other hand human genetic diabetes mellitus regularly leads to clinically apparent vascular disease and can consistently be detected by electron microscopic examination of muscle capillaries. Even in the presence of genetic diabetes mellitus, diabetic vascular disease in man appears to be independent of the severity of the carbohydrate abnormalities of diabetes. Electron microscopic evidence indicates that diabetic vascular disease regularly precedes the appearance of the overt carbohydrate derangements in adult diabetes. The overwhelming clinical importance of the vascular component of human diabetes mellitus makes it particularly important to develop a diabetic animal model in which, as in man, microangiopathy is a major component. It is, however, doubtful whether such a disease has been documented to date in any species but man. The concept which is developed from these conclusions is that it is the clinically important vascular aspect of human diabetes mellitus which is both unique to man and may well play the primary role in the pathogenesis of diabetes mellitus.

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Antibiotics

ONE OF THE REASONS for so much drug poisoning from antibiotics, is that we learned how to use them before we learned how they worked. The science of antimicrobial drugs until recently was little more than a crude screening process for mold products that could stop growth of pathogenic bacteria without gross injury to animals or human subjects. For many years nothing was known of the chemical reactions that enabled these mold products to stop growth of microbial cells, hence no one could predict whether similar reactions in human cells would be disturbed as well. One reason for this empirical approach to chemotherapy of infection was the unwillingness of drug firms in this country to invest their resources in basic analytical studies of cellular processes. To

the contrary, some companies appeared to flourish from the confusion growing from reactions and resistance to antibiotics, for it seemed to provide reason to offer new drugs with different brand names. Thanks, however, to federal support of research by a number of gifted scientists in this country and elsewhere, we now have a remarkably clear understanding of the fine structure and biochemical activity of bacterial cells, and how they are affected by antibiotics. From this understanding it should be possible to develop bacterial chemotherapy to the point where infections can be treated without drug reactions.

The key to the problem is the discovery and analysis of the bacterial cell wall. From the point of view of chemotherapy, a successful attack there can unloose the corset that holds the bacterial cell together, so that it more or less bursts from the high internal pressure. The chemical structure of the corset is like that of chitin, the substance responsible for the rigidity of the exoskeleton of insects. Sugar chains composed of acetylglucosamine and muramic acid and attached to short peptides are cross-linked to form a net-like polymer known as murein. The cross-linking reaction is carried out by an enzyme that links D-alanine to the peptide of a neighboring chain. Since penicillin is a structural analogue of D-alanyl - D-alanine, it reacts with and irreversibly inactivates the transpeptidase that functions as the cross-linking enzyme. By obstructing the terminal cross-linking reaction, this antibiotic disrupts the integrity of the murein layer and the mechanical rigidity of the cell.

These discoveries by Park, Strominger, and others, have exciting implications to clinicians who treat infections. The action of penicillin on bacterial murein means that it strikes a vulnerable bacterial target that is not present in human cells. As human cells do not contain murein and do not exhibit a cross-linking reaction involving D-alanine, penicillin cannot damage them. Penicillin thus exemplifies the ultimate in selective toxicity: lethal for the microbe and devoid of primary toxicity for the patient. Other antibiotics with the cyclic dipeptide structure of the penicillin group, such as cephalothin, exhibit the same selective toxicity.

In contrast to the penicillins, all other antimicrobial drugs attack vital structures or metabolic processes in bacteria that have a vulnerable counterpart in human cells. Polymyxin B and colistin are cationic detergents that react with phosphate groups in the cell membrane of bacteria so that

the osmotic carrier is disturbed and leakage of amino acids, purines, and pyrimidines occurs. Amphotericin B also injures the cell membrane, but through an affinity for sterols present only in fungi rather than bacteria. It is possible that the nephrotoxicity of these drugs is related to similar injury to the cell membranes of kidney epithelium. In addition, the hemolytic reactions consistently observed in patients given amphotericin B intravenously appear to result from binding of this drug to sterol groups on red cells.

The remaining drugs used for treating human infections act within the cell on synthetic and metabolic processes. The antibiotics in this group all inhibit protein synthesis. Chloramphenicol, the most toxic for humans, prevents attachment of messenger RNA to ribosomes; the tetracyclines and lincomycin interfere with binding of transfer RNA to ribosomes; and the aminoglycosides (streptomycin, kanamycin, neomycin) attach to the ribosomes and permit incorporation of incorrect amino acids in peptide chains. The effects of chloramphenicol on hemoglobin synthesis in man undoubtedly reflect the same disturbance in human cells that the drug produces in bacterial cells. Similarly the hepatotoxicity of the tetracyclines, and their ability to exaggerate azotemia, are also accountable through their ability to interfere with protein synthesis. The primary toxicity of streptomycin and kanamycin is on the eighth nerve but too little is known about the nature of this injury to speculate on its mechanism.

It is clear, therefore, that penicillin stands out from all other antibiotics in its freedom from primary toxicity in man simply because it has no biochemical target to damage. It is not surprising that penicillin can be given intravenously in doses of 60 to 80 grams with no discernible harm. Even in patients with kidney insufficiency, the toxicity from large intravenous doses is due to the potassium in penicillin, rather than to the antibiotic itself. For this reason, future hope for harmless antibiotics lies in the replacement of other antibiotics through the development of the penicillins. Research along these lines must take two major directions: a broadened antimicrobial spectrum and elimination of allergy.

Thanks to the ingenuity of the British chemists Batchelor, Dewdney, Feinberg, and Weston, exciting progress has been made in both directions. Their isolation of the penicillin nucleus 6-amino-penicillanic acid (6APA) has been followed by

brilliant success in widening its spectrum through modification of the side chain attached to 6APA. The first major development in extending the spectrum came with their synthesis of methicillin by the introduction of two methoxy groups into the side chain so that 6APA could be protected from hydrolytic inactivation by the penicillinase of resistant staphylococci. More recently they found that attaching an amino—or a carboxy—group to the side chain produced two compounds with greatly increased activity against those Gram-negative bacilli that had been clinically resistant to penicillin. Alpha-aminobenzylpenicillin (ampicillin) has been of great value in the treatment of *Salmonella*, *Proteus E. coli*, and *Hemophilus influenzae* infections, while the synthesis of alpha carboxybenzylpenicillin (carbenicillin) has made available, at last, a nontoxic drug that can be used effectively in serious *Pseudomonas* infections.

Isolation of 6APA also led to a search by its discoverers for a non-allergenic penicillin. At first 6APA was thought to be allergenic itself and hence that a nonallergenic penicillin was unlikely, but later studies by Batchelor's group disclosed that an impurity was responsible for allergy. This impurity is a conjugate of 6APA or benzylpenicillin with a protein (D-benzylpenicilloyl protein) and probably develops during manufacture. When the impurity was removed by passage through a sephadex column or by dialysis, neither benzylpenicillin nor 6APA was allergenic. This discovery and others, on the immunochemistry of penicillin allergy, offer substantial hope for the solution of the immunologic disturbances that have occurred from the use of penicillin.

In my opinion, the opportunities are so good for the eventual production of nontoxic penicillin with a universal spectrum of antibacterial activity, that other antibacterial drugs will have little usefulness. The achievement of this important goal in medicine can only come about, however, from support of research at all levels of chemotherapeutic development involving the biochemist, microbiologist, immunochemist and clinical investigator. Unfortunately the tragic restriction of federal support for medical research of this type will hold back seriously the progress that could be made in eliminating harmful reactions from antibiotic therapy.

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On a Definition of Health

THE REPORT OF THE American Medical Association's Committee on Planning and Development faces up to the important question of what is to be today's working definition of health and what is to be the role of the organized medical profession with respect to it. This report is now undergoing review by state and county medical societies and its recommendations are to be considered by the appropriate Reference Committee at the AMA Convention this June. The need to agree on a definition of health is obvious. The need becomes pressing when one considers the mounting national concern with health and the bald fact that health care is already a \$60 billion a year industry that is still growing and soon to become the largest such enterprise in the nation.

The Committee's report calls for the AMA to adopt officially the World Health Organization definition:

"Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."

The thought of such an all-encompassing definition with all its ramifications in health care stuns many physicians and other health care personnel. The traditional view has been that health means the absence of illness and that the aim of the practitioner is to restore this "health" to the afflicted patient. The word itself derives from "whole" and to heal really means to make whole. Recently, however, the concept of whole in health has been gaining significantly. Medical progress has shown that to be healthy requires that a person be in satisfactory adjustment with many and various aspects of his internal and external environment which affect him and with which he must interact. This goes somewhat beyond just the wholeness of his mind and body. It includes his physical, social, economic, cultural and even political circumstances and environment. That this is true is becoming quite clear to anyone who seeks to provide health through health care services in the urban or rural ghettos, for example, where quite evidently personal health is inseparable from the whole situation. In the further dimension of the closed earth system and its problems of population, resources, pollution, ecological balance and human behavior, the sameness of *health* and *whole* takes on yet a new meaning and a new and very pertinent reality.